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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/813,271	03/20/2001	Nico Cerletti	4-20039C/C1C1/USN	2623

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/21/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/813,271	CERLETTI, NICO	
	Examin r	Art Unit	
	David S Romeo	1647	

-- Th MAILING DATE of this communication appears on th cover sheet with th correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/776,444* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 19-25 are pending. Upon further consideration, the restriction requirement mailed December 16, 2002 (Paper No. 10) is withdrawn.

Applicant's election with traverse of Group II in Paper No. 12 is acknowledged. The traversal is moot in view of withdrawal of the restriction requirement.

Claims 19-25 are being examined.

The present application claims the benefit under 35 U.S.C. 120 of the filing date of earlier filed U.S. applications and claims the benefit under 35 U.S.C. 119 (a) of a foreign priority date. Under 35 U.S.C. 120, the claims in a U.S. application are entitled to the benefit of the filing date of an earlier filed U.S. application if the subject matter of the claim is disclosed in the manner provided by 35 U.S.C. 112, first paragraph, in the earlier filed application. Under 35 U.S.C. 119 (a) or (e), the claims in a U.S. application are entitled to the benefit of a foreign priority date or the filing date of a provisional application if the corresponding foreign application or provisional application supports the claims in the manner required by 35 U.S.C. 112, first paragraph. Support for the limitation "the process being conducted in the substantial absence of either a chaotropic agent or a copper or manganese salt" cannot be found in the earlier filed U.S. applications or in the corresponding foreign application. Accordingly, the subject matter of the present claims is not disclosed in the manner provided by 35 U.S.C. 112, first paragraph, in the earlier filed U.S. applications, and the corresponding foreign application does not support the

claims in the manner required by 35 U.S.C. 112, first paragraph. Accordingly, the subject matter of the present claims has an effective filing date of March 20, 2001, the filing date of the present application. If applicant disagrees, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to March 20, 2001 which specifically supports this particular claim limitation.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

This application repeats a substantial portion of prior Application No. 09316724, filed May 21, 1999, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19-25 are rejected under 35 U.S.C. 102(b or e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Builder (a13) in view of Rudolf (u13).

This rejection is being made under 35 U.S.C. 102(b) in the event that Applicant's priority claim is not perfected.

This rejection is being made under 35 U.S.C. 102(e) in the event that Applicant's priority claim is perfected.

Builder discloses incubating a polypeptide in a buffer of pH 7-12 comprising about 5-40% (v/v) of an alcoholic or polar aprotic solvent, about 0.2 to 3M of an alkaline earth, alkali

metal, or ammonium salt, about 0.1 to 9M of a chaotropic agent, and about 0.01 to 15 μ*M* of a copper or manganese salt, wherein an oxygen source is introduced, so that refolding of the polypeptide occurs during the incubation (paragraph bridging columns 5-6). Examples of polypeptides include TGF-β, including TGF-β1, TGF-β2, or TGF-β3 (column 8, lines 23-24). Glutathione is a suitable reducing agent (column 10, line 11). Polar aprotic solvents are such molecules as dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF) (column 11, lines 9-11). The copper or manganese may be added exogenously or may be residual from the fermentation or otherwise already present in the solution containing the polypeptide of interest (column 11, full paragraph 2). Alternatively, the copper or manganese salt is a minimal amount (column 19, full paragraph 2). The refolding is typically carried out at about 0 degrees centigrade - 45 degrees centigrade (column 20, lines 9-10). The solution optionally also contains a reducing agent (column 20, lines 17-18) at a concentration of about 0.5 mM to 8 mM (column 20, lines 24-25). Generally the concentration of chaotropic agent is about 0.1 to 9M (column 16, lines 32-33).

The metes and bounds of "substantial absence" are not clearly set forth. Conducting Builder's process in the presence of residual copper or manganese, about 0.01 to 15 μ*M* of a copper or manganese salt, or a minimal amount of copper or manganese salt is conducting the process in the substantial absence of a copper or manganese salt in the absence of evidence to the contrary. Conducting Builder's process in the presence of about 0.1 to 9M of a chaotropic agent is conducting the process in the substantial absence of a chaotropic agent in the absence of evidence to the contrary.

Builder is silent with respect to glutathione being in the reduced form. However, Rudolf teaches that reduced and oxidized glutathione are commonly used as "oxido-shuffling" reagents (page 160, full paragraph 1), indicating that Builder used reduced glutathione. In any case, Rudolf teaches that the disulfide exchange reactions, as illustrated in Eqn. 1, proceed rapidly under mildly alkaline or neutral conditions and the reaction is reversible (page 160, full paragraph 1, and first sentence of paragraph bridging pages 160-161), indicating that reduced glutathione is produced as a result and Builder's process would inherently contain glutathione in its reduced form.

Alternatively and in addition to the above, Rudolf teaches that the regeneration of native protein disulfide bonds proceeds optimally in the present of 1-3 mM reduced glutathione (paragraph bridging pages 160-161). Rudolf does not teach the refolding of TGF-βs. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to refold TGF-β in the presence of glutathione, as taught by Builder, and to modify that teaching by using reduce glutathione, as taught by Rudolf, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because reduced and oxidized glutathione are commonly used as "oxido-shuffling" reagents and because the regeneration of native protein disulfide bonds proceeds optimally in the present of 1-3 mM reduced glutathione. The invention is prima facie obvious over the prior art.

Claims 19-125 are rejected under 35 U.S.C. 102(b) as being anticipated by Cerletti (n13). The subject matter of the present claims has an effective filing date of March 20, 2001, the filing date of the present application, as discussed above. Cerletti teaches a folding process for the

preparation of biologically active, dimeric TGF-β from its denatured or otherwise non-native form. This object is achieved by treating the monomeric form of TGF-β with a folding buffer which comprises (a) a mild detergent and (b) DMSO, DMF or $DMSO_2$ or a mixture of two or three of the group consisting of DMSO, $DMSO_2$ and DMF. See page 4, last full paragraph. The term "TGF-β" is in tended to encompass TGF-β1, TGF-β2, or TGF-β3 (page 6, full paragraph 1). The denatured monomer is treated with a folding buffer which comprises an organic solvent selected from the group consisting of DMSO, DMF, $DMSO_2$ and any mixture of two or three of the group consisting of DMSO, $DMSO_2$ and DMF, at a neutral or alkaline pH and at a reasonable temperature, e.g. between about 0 degrees centigrade and about 40 degrees centigrade. A preferred pH is between about 7 and about 10, more preferred in the case of DMSO is about pH 9 to 9.5, in the case of DMF is about pH 8.5 and in the case of $DMSO_2$ is about pH 9.5. See page 8, full paragraph 2. The preferred concentration of DMSO, $DMSO_2$ or DMF for the purpose of the present invention is from about 5% to about 40%, more preferably from about 10% to about 30%. The even more preferred concentration of DMSO is about 10% to about 30%, even more preferably about 20%; for DMF the even more preferred concentration is about 10% to about 30%, even more preferably about 10%; for $DMSO_2$ the even more preferred concentration is about 10%. Mixtures of DMSO and DMF or of DMSO and $DMSO_2$ or of DMF and $DMSO_2$ can be used in a concentration of about 5% to about 40%, preferably of about 10% to about 30%, more preferably about 10% to about 20% for the solvents combined. See page 9, full paragraph 2. In a preferred embodiment of the present invention the folding buffer additionally contains a reducing substance. A suitable reducing substance which encourages the formation of disulfides in proteins or peptides is e.g. a low molecular weight sulfhydryl reagent

selected from the group consisting of glutathione in its reduced form, dithiothreitol in its reduced form, β-mercaptoethanol in its reduced form, mercaptomethanol in its reduced form, cysteine and cysteamine. However, the method also works if no such substance is present. A suitable concentration for the sulfhydryl reagent is e.g. about 1 to 100 mM, preferably about 1 to100 mM, more preferably about 2.5 mM. See page 10, full paragraph 1. Insofar as Cerletti is silent with respect to makes no mention of the presence of a copper salt or chaotropic agent and the use of a manganese salt is optional (page 9, full paragraph 1) then the process is conducted in the substantial absence of either a chaotropic agent or a copper or manganese salt.

Claims 19-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Builder (a13) in view of Rudolf (u13). The teachings of Builder (a13) in view of Rudolf (u13) are of record. See above. Builder (a13) in view of Rudolf (u13) is silent with respect to a mixture of DMSO and DMF. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to use a mixture of DMSO and DMF with a reasonable expectation of success because it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 8-23 of U.S. Patent No. 6,057,430 (b13). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the present application are generic to and fully encompass the claims of the patent.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 20-25 are indefinite because they depend from claim 54 but there is no claim 54. Hence, the claims make no sense because they are incomplete. In the interest of compact prosecution the claim will be interpreted as depending from claim 19. However, this interpretation of the claim does not relieve applicant from the requirement to respond to the instant rejection.

Claims 19-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "substantial absence" in claim 19 is a relative term which renders the claim indefinite. The term "substantial absence" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

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FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
APRIL 17, 2003